Pathophysiology of cardiogenic shock

Pietro Bertini and Fabio Guarracino

Purpose of review
We describe the pathophysiology of cardiogenic shock (CS), from the main pathways to the inflammatory mechanisms and the proteomic features.

Recent findings
Although the classical pathophysiological pathways underlying CS, namely reduced organ perfusion due to inadequate cardiac output and peripheral vasoconstriction, have been well-established for a long time, the role of macro-and micro-hemodynamics in the magnitude of the disease and its prognosis has been investigated extensively only over the last few years. Moreover, to complete the complex picture of CS pathophysiology, the study of cytokine cascade, inflammation, and proteomic analysis has been addressed recently.

Summary
Understanding the pathophysiology of CS is important to treat it optimally.

Keywords
cardiogenic shock, coupling, elastance, heart failure, pathophysiology

INTRODUCTION

Cardiogenic shock (CS) is characterized by peripheral vasoconstriction and critical end-organ damage caused by inadequate cardiac output (CO) and oxygen delivery (DO2) [1]. In general, CS involves a substantial reduction in myocardial contractility, which can lead to a potentially harmful spiral of decreased CO, low blood pressure (BP), and further coronary ischemia, both of these can lead to further contractility reductions and multiple organ failure. This loop has the potential to end in death (Fig. 1).

Identification of the underlying cause can enable the initiation of specific pharmacological or mechanical therapies after hemodynamic resuscitation and stabilization. A current registry indicated that up to 81% of patients with CS have an underlying acute coronary syndrome (ACS) [2]. Therefore, ACS should be the subject of initial diagnostic testing for patients with risk factors for coronary artery disease, and such testing should include an ECG within 10 min of presentation.

It is now well known that CS can contribute to both acute and subacute derangements of the entire circulatory system along with the peripheral vasculature. Hypoperfusion of the extremities and vital organs is also common. If the inciting event is ineffective stroke volume (SV), then peripheral vasoconstriction can maintain tissue perfusion pressure to improve coronary and peripheral perfusion while also representing increased afterload. The situation is complicated by pathological vasodilation due to systemic inflammation triggered by altered tissue perfusion and acute heart injury. Tachycardia is frequently associated and is usually assumed to be an important compensatory mechanism for the fall in SV.

PRIMARY HEART INVOLVEMENT

The classic pathogenic process is myocardial tissue damage following a significant acute myocardial infarction (AMI) leading to extreme left ventricular dysfunction [3]. Although etiologies vary, the pathophysiology of CS involves many distinct but overlapping components: an initial cardiac insult that decreases CO, central hemodynamic alterations (including changes in the interaction between pressure and volume with elevated left ventricle (LV)

Cardiothoracic and Vascular Anesthesia and Intensive Care, Department of Anesthesia and Critical Care Medicine, Azienda Ospedaliero Universitaria Pisana, Pisa, Italy

Correspondence to Fabio Guarracino, MD, Department of Anesthesia and Critical Care Medicine, Cardiothoracic and vascular anesthesia and intensive care, Azienda Ospedaliero Universitaria Pisana, Via Paradisa 2, 56123 Pisa, Italy. Tel: +39050995244;
e-mail: f.guarracino@ao-pisa.toscana.it

Curr Opin Crit Care 2021, 26:000–000
DOI:10.1097/MCC.0000000000000853

1070-5295 Copyright © 2021 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2021 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

SHOUT
SHARE
IT

KEY POINTS

- Cardiogenic shock is characterized by peripheral vasoconstriction and critical end-organ damage caused by inadequate stroke volume and oxygen delivery.
- A substantial reduction in myocardial contractility triggers the cardiogenic shock syndrome.
- Systemic inflammatory activation and reduced vascular tone can alter the classic hemodynamic features of low CO and peripheral vasoconstriction.
- Plumbing and understanding the pathophysiology on a case-by-case basis is of paramount importance to appropriately manage the syndrome.

and right ventricle (RV) filling pressures), microcirculatory instability, a systemic inflammatory reaction, and organ dysfunction [4▪▪]. These events can be considered temporal CS stages, and each of these stages can be delayed depending on the severity of the initial cardiac insult and/or early implementation of therapies [5]. Furthermore, in patients with chronic heart failure (CHF), precipitating factors [6–8] like arrhythmias or respiratory infection may cause an acute deterioration of cardiac compensation evolving to CS. Worse outcomes are described in patients with noncardiovascular precipitating factors [9].

As a consequence of an acute decrease of LV contractility, CO is reduced leading to an acute reduction of BP and subsequent increase in LV end-diastolic pressure [10]. Hypotension induces a compensatory vasoconstriction that functionally shifts blood volume into the circulating compartment contributing to elevations in cardiac filling pressures thus altering ventricular-arterial coupling (VAC) [10,11]. The systemic vasoconstriction ultimately causes an increased afterload and reduced myocardial performance. This results in a critical reduction in DO2 to the peripheral tissues and eventually the heart itself [1].

Alterations in tissue microcirculation have also been linked to 30-day mortality and temporal changes in sepsis-related organ failure assessment scores that can be improved with mechanical circulatory support (MCS) [12]. A critical reduction in cardiac power output (CPO = CO × BP) is a marker of extreme LV dysfunction, and a fall in CPO below 0.53 W is a robust indicator of bad outcome [13].

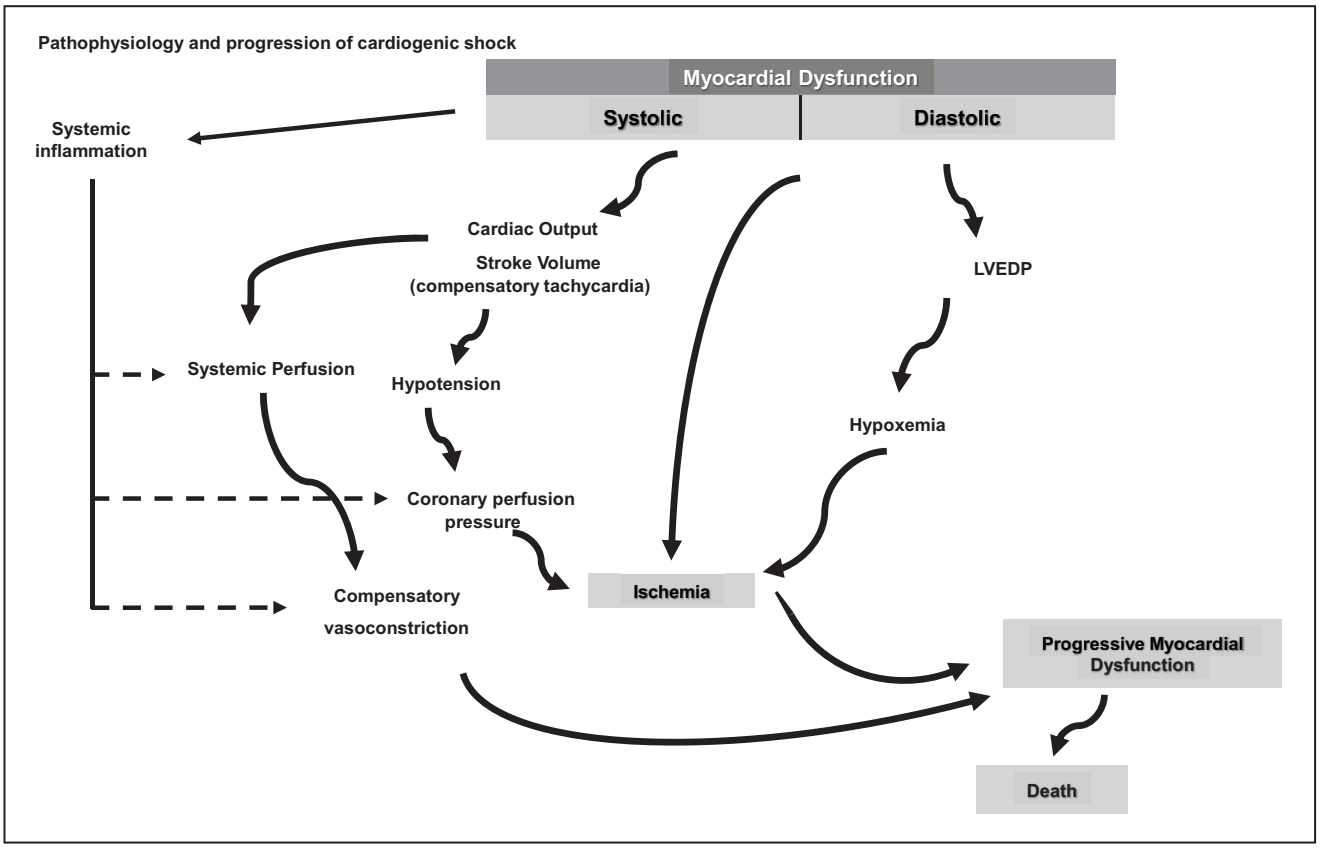

FIGURE 1. Pathophysiology and progression of cardiogenic shock.

Copyright © 2021 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

THE ROLE OF THE RIGHT VENTRICLE

The RV does not effectively tolerate acute increases in afterload because it is a 'volume pump' rather than a 'pressure pump.' RV dysfunction either due to primary contractile dysfunction or secondary preload/afterload imbalance may be primarily responsible for CS (e.g., acute pulmonary embolism, isolated primary tricuspid regurgitation, and RV cardiomyopathy). RV dysfunction may also lead to CS in combination with left-sided pathologies (e.g., inferior wall myocardial infarction-related RV infarction, extreme pulmonary hype). CS can manifest with or without pulmonary hypertension during severe RV dysfunction [4▪▪].

RV failure results in effects primarily attributed to 'venous congestion.' Because of low venous resistance, the driving pressure for venous return to the RV is low (around 5 mm Hg), but it must be maintained in RV congestion by a proportionate rise in venous pressure. To sustain venous return in CS, an abrupt increase in right atrial pressure to 15 mm Hg necessitates a tissue venous pressure close to 20 mm Hg. By lowering the perfusion pressure gradient (systemic artery pressure – venous organ pressure), this backpressure in organs significantly impairs their perfusion [14]. Therefore, insufficient forward blood flow accounts for end-organ perfusion deficits in combination with elevated venous pressures in a compromised RV. Eventually, the interventricular septum is displaced into the left ventricular space because RV failure results in RV dilatation compromising LV filling and contributing to subendocardial ischemia whose persistence can further exacerbate systemic hypoperfusion. The detection of a pulsatility index of the pulmonary artery < 0.9 identifies a significant loss of RV function [15].

THE MICROCIRCULATION INVOLVEMENT IN CS

Microcirculatory dysfunction is present early in CS patients [5]. It is associated with the development of multiorgan failure and predicts worse outcomes in patients with CS complicating AMI [12]. Global hypoperfusion induces systemic inflammation leading to a substantial NO-mediated vasodilation and a significant decrease in SVR [16,17]. Additional systemic inflammatory mediators that induce vasodilation include interleukins and tumor necrosis factor-alpha [3]. Regardless of the mechanism, these inflammatory mediators counteract certain aspects of the neurohormones resulting in a reduction in SVR and potential for venodilation, both of these can decrease BP and perpetuate the unfavorable downward spiral of CS.

Since the microcirculatory network is flow-dependent, the reduction in CO and elevated vascular tone is likely to decrease capillary responsiveness resulting in cellular hypoxia [18].

Even in extreme hypoxia, however, mitochondrial viability and function are maintained for many hours, and animal models show that mitochondrial function is initially up-regulated to meet metabolic demand [19]. Modifications in the erythrocyte nitric oxide (NO) biology of stored blood can lead to vasoconstriction, platelet accumulation, and inadequate oxygen supply; transfusions may also contribute to inflammation [20,21].

By day 2 post-CS onset, clinically overt inflammation is seen in 20–40% of CS patients, which may result in an initially low systemic vascular resistance (SVR) [22]. Immediately after the initiation of CS, elevated levels of cytokines (interleukin-1, 6, 7, 8 and 10) are observed with levels correlating to early mortality [22]. Local causes that promote vasodilation include NO-mediated pathological vasodilation, dysglycemia, and an abrupt rise in advanced glycation end-products—both of these are related to an elevated risk of death [3,23]. Unfortunately, anti-cytokine or anti NO therapies have not proved successful in CS.

A sub-analysis of the CULPRIT-SHOCK study highlighted an important and independent correlation between the variables of microcirculatory perfusion and the combined clinical outcome of 30-day all-cause death and renal replacement therapy especially in patients with a lack of hemodynamic coherence between macrocirculation and microcirculation [24▪▪]. Although it is tempting to approach the microcirculation in CS, its reaction to therapeutic stimuli is often dissociated from structural consequences; interventions aimed at normalizing the microcirculation in CS have been inconclusive [25,26].

ACUTE EXACERBATION OF CHRONIC HEART FAILURE

Between 5% and 12% of ACS cases are complicated by CS. Mechanical complications (including papillary muscle rupture, ventricular septal defect, or free wall rupture) have traditionally been known to be late complications but are usually present within 24 h of hospitalization [27,28]. For such diagnoses, a high index of suspicion and rapid echocardiography is needed.

Chronic HF may be present in an acute decompensated state and can account for up to 30% of cases of CS [29]. These patients have also experienced a decrease in the stability of the condition or have weak adherence to guideline-based treatments

1070-5295 Copyright © 2021 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2021 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

Table 1. Conditions unrelated to myocardial ischemia that can precipitate cardiogenic shock

Severe valve disease
Pericardial tamponade
Acute myocarditis
Left ventricle outflow tract obstruction
Takotsubo syndrome
Postpartum cardiomyopathy
Arrhythmias
Postcardiotomy syndrome
Sepsis
Tumors

that may cause their chronic disease to worsen acutely. The hemodynamic status and neurohormonal sensibility are often strikingly different, and thus the care of patients with chronic HF presenting in CS will vary significantly from the treatment of other forms of CS. Vasoconstrictor substances such as angiotensin II, endothelin-1, and norepinephrine are frequently profoundly upregulated in HF patients [30,31].

OTHER FACTORS CONTRIBUTING TO CARDIOGENIC SHOCK

Other conditions can destabilize and exacerbate CS (Table 1). Advanced valvular heart disease and prosthetic dysfunction can present as CS mainly if they were previously undetected or under-monitored though this is becoming less likely as echocardiographic techniques and surveillance have improved [32–34]. Paradoxically, in acute myocarditis, the sickest patients on presentation have the best chances of recovery particularly in younger groups [35]. Rapid identification of the clinical syndrome and prompt activation of aggressive hemodynamic support may be crucial for survival [36–38].

Stress-induced cardiomyopathy or Takotsubo syndrome is increasingly known, and it has been associated with CS and can involve MCS although it sometimes presents with mild cardiovascular compromise. The LV dysfunction is usually transient in this syndrome [39–41].

Circulatory collapse may also be caused by hyperthyroidism and hypothyroidism [42,43]. Cardiac disorders associated with pregnancy including both peripartum cardiomyopathy and acute coronary dissection can present as CS. Numerous additional causes of CS have been identified, but these usually occur only in $< 1\%$ of patients [44,45].

Postcardiotomy shock affects 2–6% of patients who have undergone cardiac surgery [46,47]. This may be due to poor CO (resulting in myocardial hibernation, stunning or insufficient cardioprotection), systemic vasodilation, or any of these conditions [48].

About 20–30% of CS cases are complicated by infection [49].

Multiorgan dysfunction in sepsis or septic shock is the result of both macro-hemodynamic alterations and microcirculatory dysfunction and portends a poor prognosis [4▪▪,50,51]. Myocardial depression is a well-recognized factor contributing to the hemodynamic alteration in septic patients [52] and characterizes septic cardiomyopathy. Several myocardial depressant factors have been identified including inflammation and pathogen-associated factors. However, a key pathophysiological element seems to be endothelial dysfunction caused by increased endothelial permeability related to inflammation and leading to cardiomyocyte edema and dysfunction [53▪]. Moreover, mechanisms related to altered NO metabolism, oxidative stress, mitochondrial dysfunction, autonomic dysregulation, and abnormal calcium trafficking have all been considered to play a role [52].

Microcirculatory injury in the intestinal barrier contributes to increased bacterial translocation, and the gut tends to be one of the first organs to be affected by shock [54,55]. Lipopolysaccharide (endotoxins) produced by gram-negative bacteria enter the bloodstream and lead to the development and inflammation of cytokines [50] thus precipitating hemodynamics until multiorgan failure [56]. Moreover, cardio-depressant sedatives (e.g., propofol), antiarrhythmics, beta-blockers, improper use of diuretics, and excessive volume loading in RV shock are all iatrogenic causes that may lead to a cardiovascular malfunction in CS [4▪▪,57].

THE CROSS-TALK BETWEEN THE HEART AND THE CIRCULATION

Bedside pressure–volume (PV) measurement has increasingly been used in clinical practice to better explain the pathophysiology of CS and customize its treatment [58].

The PV loop is contained within the constraints of the end-systolic and end-diastolic pressure-volume relationships (ESPVR and EDPVR) (Fig. 2A). The ESPVR shifts downward and rightward when a rapid drop in ventricular contractility occurs. BP (reduced height of the PV loop), SV (reduced width of the PV loop), and CO are all automatically and greatly reduced as a result of this decrease (Fig. 2B). Elevations of LV end-diastolic pressure and PCWP may also be seen.

The slope of the ESPVR is called LV elastance (Elv) and can be assimilated to LV contractility. The slope of the line connecting end-systolic volume/

Copyright © 2021 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

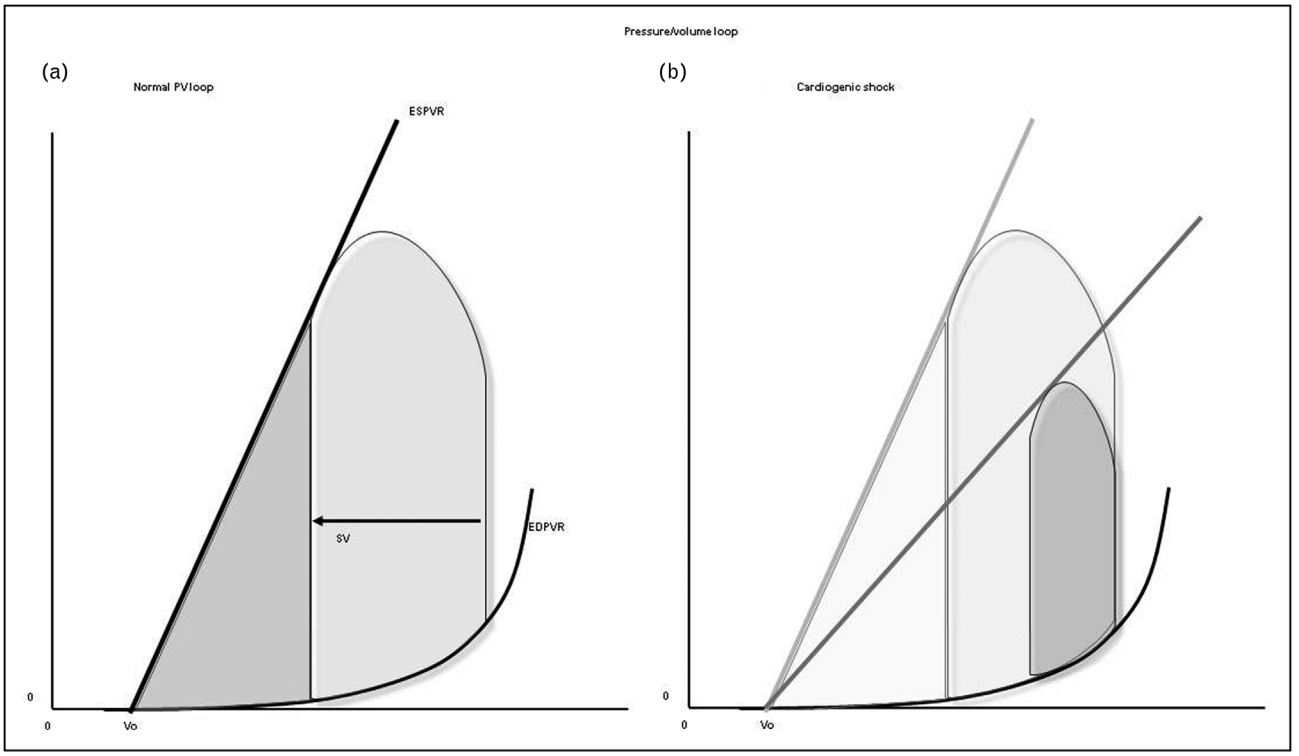

FIGURE 2. Pressure/volume loop. A: Normal pressure-volume loop (EDPVR, end diastolic pressure-volume relationship; ESPVR, end systolic pressure-volume relationship; SV, stroke volume). B: Pressure volume loop in Cardiogenic Shock.

pressure points in the PV plane and end-diastolic volume/zero pressure points is called the arterial elastance (Ea) and is correlated with afterload. The relationship between Ea and Elv is called VAC (Fig. 3), and its value is near unity in physiologic conditions. In acutely altered hemodynamic states, however, reduction of contractility and/or increase in afterload lead to VAC augmentation and increased myocardial oxygen consumption [59,60].

The utility of VAC assessment in the acute CS state still needs to be explored. However, our experience on the bedside assessment of VAC in septic shock patients [61] and in tracking and predicting hemodynamic responses to treatment [62] suggests that research on the bedside assessment of elastances and VAC in CS is advocated. Assessing the heart-circulation interaction allows a deep understanding of the pathophysiology behind the data obtained from the hemodynamic monitoring and supports management and reassessment.

Baroreceptors sense decreases in BP and cause efferent autonomic nerve fibers to release epinephrine from the adrenal glands. These factors boost heart rate (CO), increase cardiac contractility, and cause systemic vasoconstriction.

Venoconstriction is also a crucial component in the pathophysiology of CS. It induces a leftward change in the venous pressure-volume curve, which functionally moves blood from an unstressed to a stressed compartment thus increasing functional circulating blood volume and raising central and

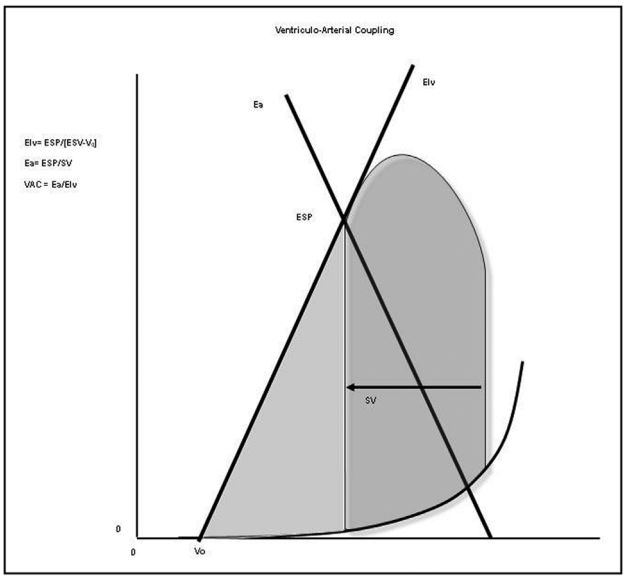

FIGURE 3. Ventriculo-arterial coupling. Ea, arterial elastance; Elv, ventricular elastance; ESP, end systolic pressure; SV, stroke volume; V_O, volume at theoretical zero pressure; VAC, ventriculo-arterial coupling.

1070-5295 Copyright © 2021 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2021 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

pulmonary venous pressures. Furthermore, these effects result in further rightward movements of the PV loop, elevated BP, and negligible effects on the CO. CO at this point is more subject to increases driven by heart rate increment [10].

Remodeling is driven by persistent neurohormonal activation and elevated filling pressures and is characterized by progressive increases in LV size and reductions in function. In the PV plane, remodeling manifests as rightward shifts of both the ESPVR and the EDPVR and is expressed in CHF's global changes in LV size, structure, and function (Fig. 3C) [63].

WHAT IS NEW AND WHERE TO GO FROM HERE

Proteomic research may help better understand pathophysiology, improve risk stratification, and develop new treatments. Recent research discovered a four-protein complex (CS4P) linked to multiorgan dysfunction, systemic inflammation, and immune activation. Changes in the expression of CS4P during the early hours of CS will precede overt multiorgan failure and classify patients at higher risk of mortality [64]. Furthermore, higher levels of circulating dipeptidyl peptidase 3 (DPP-3) were related to worsening hemodynamics, refractory CS, and 90-day mortality [65▪,66▪].

DPP-3 is a cytosolic enzyme associated with inflammatory pathway alterations that cause a significant inotropic and negative vasodilatory effect [65▪], which can be reversed in animal models [64,66▪].

CONCLUSION

CS is a well-established entity leading to hemodynamic collapse and death. Pathophysiological reasoning and understanding are the cornerstones of appropriate therapeutic planning and clinical management. Properly identifying hemodynamic phenotypes and understanding the role of cytokines and inflammatory mediators is paramount to avoid misinterpretation of hemodynamic variables, prevent derangement, and limit mortality. Research on the pathophysiological role of heart-circulation interactions and cellular and proteomic mechanisms is advocated to better target understanding of the pathways leading to CS and better tailor future therapeutic efforts.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

F.G. has received speaker fees and consultancy honoraria from Amomed, Baxter, Edwards, Masimo, Orion Pharma, and Teleflex

For the remaining author, none were declared.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ▪ of special interest
- ▪▪ of outstanding interest

1. van Diepen S, Katz JN, Albert NM, *et al.* Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. Circulation 2017; 136:e232–e268.
2. Harjola V-P, Lassus J, Sionis A, *et al.* Clinical picture and risk prediction of short-term mortality in cardiogenic shock. Eur J Heart Fail 2015; 17:501–509.
3. Hochman JS. Cardiogenic shock complicating acute myocardial infarction: expanding the paradigm. Circulation 2003; 107:2998–3002.
4. ▪▪ Chioncel O, Parissis J, Mebazaa A, *et al.* Epidemiology, pathophysiology and contemporary management of cardiogenic shock – a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2020; 22:1315–1341.

Latest statement on cardiogenic shock from the European Society of Cardiology. It includes a clear summary of the pathophysiological feature of this syndrome.

5. De Backer D, Creteur J, Dubois M-J, *et al.* Microvascular alterations in patients with acute severe heart failure and cardiogenic shock. Am Heart J 2004; 147:91–99.
6. Platz E, Jhund PS, Claggett BL, *et al.* Prevalence and prognostic importance of precipitating factors leading to heart failure hospitalization: recurrent hospitalizations and mortality. Eur J Heart Fail 2018; 20:295–303.
7. Arrigo M, Tolppanen H, Sadoune M, *et al.* Effect of precipitating factors of acute heart failure on readmission and long-term mortality. ESC Heart Fail 2016; 3:115–121.
8. Arrigo M, Gayat E, Parenica J, *et al.* Precipitating factors and 90-day outcome of acute heart failure: a report from the intercontinental GREAT registry. Eur J Heart Fail 2017; 19:201–208.
9. Shpektor A. Cardiogenic shock: the role of inflammation. Acute Card Care 2010; 12:115–118.
10. Furer A, Wessler J, Burkhoff D. Hemodynamics of cardiogenic shock. Interv Cardiol Clin 2017; 6:359–371.
11. Trambaiolo P, Bertini P, Borrelli N, *et al.* Evaluation of ventriculo-arterial coupling in ST elevation myocardial infarction with left ventricular dysfunction treated with levosimendan. Int J Cardiol 2019; 288:1–4.
12. den Uil CA, Lagrand WK, van der Ent M, *et al.* Impaired microcirculation predicts poor outcome of patients with acute myocardial infarction complicated by cardiogenic shock. Eur Heart J 2010; 31:3032–3039.
13. Fincke R, Hochman JS, Lowe AM, *et al.* Cardiac power is the strongest hemodynamic correlate of mortality in cardiogenic shock: a report from the SHOCK trial registry. J Am Coll Cardiol 2004; 44:340–348.
14. Verbrugge FH, Dupont M, Steels P, *et al.* Abdominal contributions to cardiorenal dysfunction in congestive heart failure. J Am Coll Cardiol 2013; 62:485–495.
15. Korabathina R, Heffernan KS, Paruchuri V, *et al.* The pulmonary artery pulsatility index identifies severe right ventricular dysfunction in acute inferior myocardial infarction. Catheter Cardiovasc Interv 2012; 80:593–600.
16. Thiele H, Allam B, Chatellier G, *et al.* Shock in acute myocardial infarction: the Cape Horn for trials? Eur Heart J 2010; 31:1828–1835.
17. Reyentovich A, Barghash MH, Hochman JS. Management of refractory cardiogenic shock. Nat Rev Cardiol 2016; 13:481–492.
18. Kirschenbaum LA, Astiz ME, Rackow EC, *et al.* Microvascular response in patients with cardiogenic shock. Crit Care Med 2000; 28:1290–1294.
19. Honda HM, Korge P, Weiss JN. Mitochondria and ischemia/reperfusion injury. Ann NY Acad Sci 2005; 1047:248–258.
20. Ndrepepa G, Berger PB, Mehilli J, *et al.* Periprocedural bleeding and 1-year outcome after percutaneous coronary interventions: appropriateness of including bleeding as a component of a quadruple end point. J Am Coll Cardiol 2008; 51:690–697.
21. Rao SV, Jollis JG, Harrington RA, *et al.* Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. JAMA 2004; 292:1555–1562.
22. Prondzinsky R, Unverzagt S, Lemm H, *et al.* Interleukin-6, -7, -8 and -10 predict outcome in acute myocardial infarction complicated by cardiogenic shock. Clin Res Cardiol 2012; 101:375–384.
23. Selejan S-R, Pöss J, Hewera L, *et al.* Role of receptor for advanced glycation end products in cardiogenic shock. Crit Care Med 2012; 40:1513–1522.

Copyright © 2021 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

24. Wijntjens GW, Fengler K, Fuernau G, *et al.* Prognostic implications of ■■ microcirculatory perfusion versus macrocirculatory perfusion in cardiogenic shock: a CULPRIT-SHOCK substudy. Eur Heart J Acute Cardiovasc Care 2020; 9:108–119.
CULPRIT-SHOCK spinoff explaining macrocirculatory vs microcirculatory perfusion alteration in cardiogenic shock and its prognostic implications.
25. De Backer D, Ortiz JA, Salgado D. Coupling microcirculation to systemic hemodynamics. Curr Opin Crit Care 2010; 16:250–254.
26. Du Z, Jia Z, Wang J, *et al.* Effect of increasing mean arterial blood pressure on microcirculation in patients with cardiogenic shock supported by extracorporeal membrane oxygenation. Clin Hemorheol Microcirc 2018; 70:27–37.
27. Kutty RS, Jones N, Moorjani N. Mechanical complications of acute myocardial infarction. Cardiol Clin 2013; 31:519–531vii-viii.
28. Kohsaka S, Menon V, Lowe AM, *et al.* Systemic inflammatory response syndrome after acute myocardial infarction complicated by cardiogenic shock. Arch Intern Med 2005; 165:1643–1650.
29. Kar B, Gregoric ID, Basra SS, *et al.* The percutaneous ventricular assist device in severe refractory cardiogenic shock. J Am Coll Cardiol 2011; 57:688–696.
30. Shah M, Ali V, Lamba S, *et al.* Pathophysiology and clinical spectrum of acute congestive heart failure. Rev Cardiovasc Med 2001; 2(Suppl 2): S2–6.
31. Milo-Cotter O, Cotter-Davison B, Lombardi C, *et al.* Neurohormonal activation in acute heart failure: results from VERITAS. Cardiology 2011; 119:96–105.
32. Otto CM. Calcific aortic valve disease: new concepts. Semin Thorac Cardiovasc Surg 2010; 22:276–284.
33. Wilson N. Rheumatic heart disease in indigenous populations–New Zealand experience. Heart Lung Circ 2010; 19:282–288.
34. De Bonis M, Maisano F, La Canna G, *et al.* Treatment and management of mitral regurgitation. Nat Rev Cardiol 2011; 9:133–146.
35. McCarthy RE, Boehmer JP, Hruban RH, *et al.* Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. N Engl J Med 2000; 342:690–695.
36. Mody KP, Takayama H, Landes E, *et al.* Acute mechanical circulatory support for fulminant myocarditis complicated by cardiogenic shock. J Cardiovasc Transl Res 2014; 7:156–164.
37. Chen Y-S, Yu H-Y, Huang S-C, *et al.* Experience and result of extracorporeal membrane oxygenation in treating fulminant myocarditis with shock: what mechanical support should be considered first? J Heart Lung Transplant 2005; 24:81–87.
38. Mirabel M, Luyt C-E, Leprince P, *et al.* Outcomes, long-term quality of life, and psychologic assessment of fulminant myocarditis patients rescued by mechanical circulatory support. Crit Care Med 2011; 39:1029–1035.
39. Elesber AA, Prasad A, Lennon RJ, *et al.* Four-year recurrence rate and prognosis of the apical ballooning syndrome. J Am Coll Cardiol 2007; 50:448–452.
40. Parodi G, Bellandi B, Del Pace S, *et al.* Natural history of tako-tsubo cardiomyopathy. Chest 2011; 139:887–892.
41. Sharkey SW, Windenburg DC, Lesser JR, *et al.* Natural history and expansive clinical profile of stress (tako-tsubo) cardiomyopathy. J Am Coll Cardiol 2010; 55:333–341.
42. Ertek S, Cicero AF. Hyperthyroidism and cardiovascular complications: a narrative review on the basis of pathophysiology. Arch Med Sci 2013; 9:944–952.
43. Mathew V, Misgar RA, Ghosh S, *et al.* Myxedema coma: a new look into an old crisis. J Thyroid Res 2011; 2011:1–7.
44. Huffman C, Wagman G, Fudim M, *et al.* Reversible cardiomyopathies–a review. Transplant Proc 2010; 42:3673–3678.
45. Haghikia A, Podewski E, Libhaber E, *et al.* Phenotyping and outcome on contemporary management in a German cohort of patients with peripartum cardiomyopathy. Basic Res Cardiol 2013; 108:366–378.
46. Hausmann H, Potapov EV, Koster A, *et al.* Prognosis after the implantation of an intra-aortic balloon pump in cardiac surgery calculated with a new score. Circulation 2002; 106:I203–206.
47. Mohite PN, Sabashnikov A, Patil NP, *et al.* Short-term ventricular assist device in postcardiotomy cardiogenic shock: factors influencing survival. J Artif Organs 2014; 17:228–235.
48. Torchiana DF, Hirsch G, Buckley MJ, *et al.* Intraaortic balloon pumping for cardiac support: trends in practice and outcome, 1968 to 1995. J Thorac Cardiovasc Surg 1997; 113:758–764discussion 764-769.
49. Parenica J, Jarkovsky J, Malaska J, *et al.* Infectious complications and immune/inflammatory response in cardiogenic shock patients: a prospective observational study. Shock 2017; 47:165–174.
50. Harjola V-P, Mullens W, Banaszewski M, *et al.* Organ dysfunction, injury and failure in acute heart failure: from pathophysiology to diagnosis and management. A review on behalf of the Acute Heart Failure Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur J Heart Fail 2017; 19:821–836.
51. Moore JPR, Dyson A, Singer M, *et al.* Microcirculatory dysfunction and resuscitation: why, when, and how. Br J Anaesth 2015; 115:366–375.
52. Ehrman RR, Sullivan AN, Favot MJ, *et al.* Pathophysiology, echocardiographic evaluation, biomarker findings, and prognostic implications of septic cardiomyopathy: a review of the literature. Crit Care 2018; 22:112–125.
53. L'Heureux M, Sternberg M, Brath L, *et al.* Sepsis-induced cardiomyopathy: a ■ comprehensive review. Curr Cardiol Rep 2020; 22:35–46.
This review offers an updated and comprehensive description of the pathogenesis and pathophysiology of septic cardiomyopathy.
54. Schlag G, Redl H, Hallström S. The cell in shock: the origin of multiple organ failure. Resuscitation 1991; 21:137–180.
55. Nagatomo Y, Tang WHW. Intersections between microbiome and heart failure: revisiting the gut hypothesis. J Card Fail 2015; 21:973–980.
56. Bertini P, Guarracino F. Septic shock and the heart. Curr Anesthesiol Rep 2019; 9:165–173.
57. Benjamin EJ, Blaha MJ, Chiuve SE, *et al.* Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation 2017; 135:e146–e603.
58. Chen CH, Fetics B, Nevo E, *et al.* Noninvasive single-beat determination of left ventricular end-systolic elastance in humans. J Am Coll Cardiol 2001; 38:2028–2034.
59. Nieminen MS, Buerke M, Cohen-Solál A, *et al.* The role of levosimendan in acute heart failure complicating acute coronary syndrome: a review and expert consensus opinion. Int J Cardiol 2016; 218:150–157.
60. Guarracino F, Baldassarri R, Pinsky MR. Ventriculo-arterial decoupling in acutely altered hemodynamic states. Crit Care 2013; 17:213–219.
61. Guarracino F, Ferro B, Morelli A, *et al.* Ventriculoarterial decoupling in human septic shock. Crit Care 2014; 18:R80.
62. Guarracino F, Bertini P, Pinsky MR. Cardiovascular determinants of resuscitation from sepsis and septic shock. Crit Care 2019; 23:118–130.
63. Pfeffer MA, Pfeffer JM, Fishbein MC, *et al.* Myocardial infarct size and ventricular function in rats. Circ Res 1979; 44:503–512.
64. Rueda F, Borràs E, García-García C, *et al.* Protein-based cardiogenic shock patient classifier. Eur Heart J 2019; 40:2684–2694.
65. Takagi K, Blet A, Levy B, *et al.* Circulating dipeptidyl peptidase 3 and alteration ■ in haemodynamics in cardiogenic shock: results from the OptimaCC trial. Eur J Heart Fail 2020; 22:279–286.
This study offers an interesting insight into the role of dipeptidyl peptidase 3 in cardiogenic shock.
66. Deniau B, Rehfeld L, Santos K, *et al.* Circulating dipeptidyl peptidase 3 is a ■ myocardial depressant factor: dipeptidyl peptidase 3 inhibition rapidly and sustainably improves haemodynamics. Eur J Heart Fail 2020; 22:290–299.
This study interestingly highlights the myocardial depressant action of dipeptidyl peptidase 3 in cardiogenic shock and offers a new perspective on the treatment consisting in its inhibition.

1070-5295 Copyright © 2021 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2021 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.